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☐ 1. Document ID: US 5948682 A
Entry 1 of 4 File: USPT Sep 7, 1999

US-PAT-NO: 5948682
DOCUMENT-IDENTIFIER: US 5948682 A
TITLE: Preparation of heterologous proteins on oil bodies

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

☐ 2. Document ID: US 5830448 A
Entry 2 of 4 File: USPT Nov 3, 1998

US-PAT-NO: 5830448
DOCUMENT-IDENTIFIER: US 5830448 A
TITLE: Compositions and methods for the treatment of tumors

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

☐ 3. Document ID: US 5843705 A
Entry 3 of 4 File: USPT Dec 1, 1998

US-PAT-NO: 5843705
DOCUMENT-IDENTIFIER: US 5843705 A
TITLE: Transgenically produced antithrombin III

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

☐ 4. Document ID: US 5762921 A
Entry 4 of 4 File: USPT Jun 9, 1998

US-PAT-NO: 5762921
DOCUMENT-IDENTIFIER: US 5762921 A
TITLE: Composition and methods for the treatment of tumors

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

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l2 and monosaccharide	4

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Content Information for 09/143155

Search Another: Serial# [ ] Search **or Patent#** [ ] Search

Num	Type	Date	Code	Contents Description
7	D	12/13/1999	DOCK	DATE CASE WAS DOCKETED
6	I	12/02/1998	M844	PRIOR ART CITATION FILED P/E
5	D	10/24/1998	DOCK	DATE CASE WAS DOCKETED
4	I	08/28/1998	A.PE	PRE-EXAMINATION AMENDMENT
3	I	09/22/1998	OIPE	APPLICATION DISPATCHED FROM PRE-EXAM
2	E	09/08/1998	SCAN	APPLICATION SCANNED AND DISPATCHED FROM PRE-EXAM
1	E	09/03/1998	IEXX	INITIAL EXAM TEAM XX

Serial Info | **Contents** | Attorney/Agent Info | Continuity Data | Foreign Data | Inventors | Address | Fees

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L3 ANSWER 1 OF 24 CAPLUS COPYRIGHT 1999 ACS
AN 1999:656017 CAPLUS
DN 131:282377
TI Engineering protein posttranslational modification in **transgenic** non-human mammals
IN Lubon, Henryk; Drohan, William N.; Paleyanda, Rekha K.
PA American Red Cross, USA
SO U.S., 20 pp., Cont.-in-part of U.S. 5,589,604.
CODEN: USXXAM
DT Patent
LA English
IC ICM A01K067-00
ICS A01K067-027; C12P021-04; C12P021-06
NCL 800014000
CC 3-1 (Biochemical Genetics)
FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5965789	A	19991012	US 1995-434834	19950504
	US 5831141	A	19981103	US 1992-943246	19920910
	US 5589604	A	19961231	US 1994-247484	19940523
	WO 9634966	A2	19961107	WO 1996-US6121	19960506
	W: AU, CA, JP, MX				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2220109	AA	19961107	CA 1996-2220109	19960506
	AU 9663474	A1	19961121	AU 1996-63474	19960506

PRAI	US 1991-638995	19910111
	US 1992-943246	19920910
	US 1994-198068	19940208
	US 1994-247484	19940523
	US 1995-434834	19950504
	WO 1996-US6121	19960506

AB The invention relates to **transgenic** non-human multicellular organisms that contain polynucleotides for expressing proteins that alter posttranslational modification. In particular, the invention provides multiply-**transgenic** animals in which a first **transgene** encodes a first protein, a second **transgene** encodes a second protein, and expression of the second protein affects the posttranslational modification of the first protein in cells of said organism. Expression in preferred embodiments is in specific cells and the modified protein is secreted into a bodily fluid. An example provides **transgenic** mice which produce human protein C and the processing protease PACE/furin in mammary glands and secrete both proteins into milk. The protein C and furin genes are expressed from the mammary gland-specific promoter for whey acidic protein.
ST **transgenic** mammal protein manuf posttranslational modification; mouse **transgenic** protein C furin secretion milk
IT Proteins (specific proteins and subclasses)
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BPR (Biological process); BIOL (Biological study); PREP (Preparation); PROC (Process)
(Gas6 (growth arrest-specific, 6); engineering protein posttranslational modification in **transgenic** non-human mammals)
IT Matrix proteins
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BPR (Biological process); BIOL (Biological study); PREP (Preparation); PROC

(Process)
(MGP (matrix .gamma.-carboxyglutamic acid-contg. protein); engineering protein posttranslational modification in **transgenic** non-human mammals)

IT Cattle
Goat
Guinea pig (Cavia porcellus)
Hamster
Mammal (Mammalia)
Mouse
Post-translational processing
Rabbit
Rat
Sheep
Swine
(engineering protein posttranslational modification in **transgenic** non-human mammals)

IT Proteins (general), preparation
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(engineering protein posttranslational modification in **transgenic** non-human mammals)

IT Albumins, biological studies
Fibrinogens
Immunoglobulins
Osteocalcins
Protein S (blood coagulation factor)
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BPR (Biological process); BIOL (Biological study); PREP (Preparation); PROC (Process)
(engineering protein posttranslational modification in **transgenic** non-human mammals)

IT Mammary gland
(protein manuf. in; engineering protein posttranslational modification in **transgenic** non-human mammals)

IT Milk
(protein secretion into; engineering protein posttranslational modification in **transgenic** non-human mammals)

IT Enzymes, biological studies
RL: BPN (Biosynthetic preparation); BPR (Biological process); BIOL (Biological study); PREP (Preparation); PROC (Process)
(.gamma.-carboxylating; engineering protein posttranslational modification in **transgenic** non-human mammals)

IT 9000-94-6P, **Antithrombin III** 9001-25-6P, Blood-coagulation factor VII 9001-26-7P, Prothrombin 9001-28-9P, Blood-coagulation factor IX 9001-29-0P, Blood-coagulation factor X 11096-26-7P, Erythropoietin 60202-16-6P, Protein C 113189-02-9P, Blood-coagulation factor VIII 139639-23-9P, Tissue-type plasminogen activator
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BPR (Biological process); BIOL (Biological study); PREP (Preparation); PROC (Process)
(engineering protein posttranslational modification in **transgenic** non-human mammals)

IT 141760-45-4P, Furin
RL: BPN (Biosynthetic preparation); BPR (Biological process); BIOL (Biological study); PREP (Preparation); PROC (Process)
(engineering protein posttranslational modification in **transgenic** non-human mammals)

IT 246038-41-5 246038-42-6
RL: PRP (Properties)
(unclaimed nucleotide sequence; engineering protein posttranslational modification in **transgenic** non-human mammals)

IT 246038-43-7
RL: PRP (Properties)
(unclaimed protein sequence; engineering protein posttranslational

modification in **transgenic** non-human mammals)
IT. 245724-26-9 245724-27-0 245724-28-1 245724-29-2
RL: PRP (Properties)
(unclaimed sequence; engineering protein posttranslational modification

L3 ANSWER 8 OF 24 CAPLUS COPYRIGHT 1999 ACS
AN 1998:75490 CAPLUS
DN 128:166377
TI Commercialization of proteins produced in the mammary gland
AU Ziomek, C. A.
CS Genzyme Transgenics Corporation (GTC), Framingham, MA, USA
SO Theriogenology (1998), 49(1), 139-144
CODEN: THGNBO; ISSN: 0093-691X
PB Elsevier Science Inc.
DT Journal; General Review
LA English
CC 16-0 (Fermentation and Bioindustrial Chemistry)
Section cross-reference(s): 3, 13
AB A review with 14 refs. In the mid 1980's, a few pioneering companies undertook the risk of developing methodologies for the prodn. of complex human therapeutic proteins in the milk of **transgenic** animals. As we approach the end of the 1990's, the prospect of achieving this aim is becoming a reality as the first of these human therapeutic products, **antithrombin III** and alpha-I-antitrypsin are making their way through human clin. trials. It is projected that licensure by the Regulatory agencies and market launch for these **transgenically** produced therapeutics will occur around the year 2000. Although much has already been achieved, addnl. **transgenic** challenges await the basic embryo researcher and practitioner. The biopharming community recognizes the need for addnl. innovative methodologies (such as cloning, sperm sexing and retroviral mediated gene transfer etc.) to overcome the natural biol. barriers and increase the efficiency of **transgenic** dairy animal prodn. and rapid herd expansion.
ST review protein prodn mammary gland
IT Mammary gland
Transformation (genetic method)
(commercialization of proteins produced in mammary gland)
IT **Transgenes**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(commercialization of proteins produced in mammary gland)
IT Proteins (general), preparation
RL: BMF (Bioindustrial manufacture); BIOL (Biological study); PREP (Preparation)
(the

L3 ANSWER 12 OF 24 CAPLUS COPYRIGHT 1999 ACS
AN 1997:489900 CAPLUS
TI Therapeutic proteins from the milk of **transgenic** livestock: Biosynthesis, purification and safety issues.
AU Velander, William H.
CS Department Chemical Engineering, Virginia Tech, Blacksburg, VA, 24061, USA
SO Book of Abstracts, 214th ACS National Meeting, Las Vegas, NV, September 7-11 (1997), MEDI-143 Publisher: American Chemical Society, Washington, D. C.
CODEN: 64RNAO
DT Conference; Meeting Abstract
LA English
AB The mammary gland of **transgenic** livestock has been shown to be a prodigious bioreactor for making complex, recombinant therapeutic proteins. Recombinant human Protein C, Factor IX, Factor VIII, Fibrinogen, **Antithrombin III**, and Alpha1-antitrypsin have been produced in the milk of pigs, goats and sheep. Two of these proteins are currently in human clin. trials. The United States Food and Drug Administration has issued a "points to consider document" that addresses key regulatory issues facing the manuf. and testing of human therapeutics derived from **transgenic** animals. As with other biologics, issues concerning product safety and efficacy are centered about reproducibility of the therapeutic product and pathogen safety. Reproducibility is reflected in several examples of genotypic and phenotypic stability which have been shown in **transgenic** livestock. The potential for zoonotic disease transmission is species specific among livestock. The mammary gland has been shown to be capable of making a diversity of post-translational modifications. However, rate limitations in glycosylation, gamma-carboxylation of glutamic acid, propeptide removal and intra-chain proteolytic processing have been shown to occur. Unlike many mammalian cell types, immature forms of the recombinant protein appear to be freely secreted by mammary epithelial cells. Simplified, nonaffinity, scaleable processes can be used to purify active recombinant proteins from milk, in spite of the presence of immature recombinant and endogenous proteins.

L3 ANSWER 13 OF 24 CAPLUS COPYRIGHT 1999 ACS
AN 1997:413673 CAPLUS
DN 127:148357
TI The past, present, and future of **transgenic** bioreactors
AU Drohan, William N.
CS J. Holland Laboratory, American Red Cross, Rockville, MD, 20855, USA
SO Thromb. Haemostasis (1997), 78(1), 543-547
CODEN: THHADQ; ISSN: 0340-6245
PB Schattauer
DT Journal; General Review
LA English
CC 16-0 (Fermentation and Bioindustrial Chemistry)
Section cross-reference(s): 3
AB A review is given with 57 refs. Hybrid genes can control the tissue-specific synthesis of human proteins in **transgenic** animals. It is now possible to produce proteins of biomedical value in the body fluids or cells of **transgenic** livestock. The 1st **transgenically** produced protein, **antithrombin III**, is now in clin. trials and others will soon follow.
ST review **transgenic** animal protein bioreactor
IT Bioreactors

Transformation (genetic method)
(**transgenic** animals and bioreactors, protein prodn.)

IT Proteins (general), preparation
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(**transgenic** animals and bioreactors, protein prodn.)

L6 ANSWER 9 OF 14 MEDLINE
AN 86104195 MEDLINE
DN 86104195
TI Contribution of **monosaccharide** residues in heparin binding to **antithrombin III.**
AU Atha D H; Lormeau J C; Petitou M; Rosenberg R D; Choay J
NC PO1-HL33014 (NHLBI)
SO BIOCHEMISTRY, (1985 Nov 5) 24 (23) 6723-9.
Journal code: A0G. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198605
AB The importance of 3-O- and 6-O-sulfated glucosamine residues within the heparin octasaccharide iduronic acid(1)----N-acetylglucosamine 6-O-sulfate(2)----glucuronic acid(3)----N-sulfated glucosamine 3,6-di-O-sulfate(4)----iduronic acid 2-O-sulfate(5)----N-sulfated glucosamine 6-O-sulfate(6)----iduronic acid 2-O-sulfate(7)----anhydromannitol 6-O-sulfate(8) was determined by comparing with synthetic tetra- and penta-saccharides its ability to bind human antithrombin. The octasaccharide had an affinity for antithrombin of 1 X 10(-8) M (10.2 kcal/mol) measured by intrinsic fluorescence enhancement at 6 degrees C. The synthetic pentasaccharide, consisting of residues 2-6, had an affinity of 3 X 10(-8) M (9.6 kcal/mol). The same pentasaccharide, except lacking the 3-O-sulfate on residue 4, had an affinity of 5 X 10(-4) M (4.5 kcal/mol) measured by equilibrium dialysis. The tetrasaccharide, consisting of residues 2-5, bound antithrombin with an affinity of 5 X 10(-6) M (6.8 kcal/mol). The tetrasaccharide, consisting of residues 3-6, had an affinity of 5 X 10(-5) M (5.5 kcal/mol). Since the loss of either the 6-O-sulfated residue 2 or the 3-O-sulfate of residue 4 results in a 4-5 kcal/mol or a 40-50% loss in binding energy of the pentasaccharide, these two residues must be the major contributors to the binding and must be linked to the biologic activity of the octasaccharide.
CT Check Tags: Animal; Support, U.S. Gov't, P.H.S.
Antithrombin III: IP, isolation & purification
***Antithrombin III: ME, metabolism**
Calorimetry
Carbohydrate Sequence
Cattle
Heparin: IP, isolation & purification
*Heparin: ME, metabolism
Indicators and Reagents
Intestinal Mucosa: ME, metabolism
Oligosaccharides: AN, analysis
*Oligosaccharides: CS, chemical synthesis
Spectrometry, Fluorescence
Swine
RN **9000-94-6 (Antithrombin III)**; 9005-49-6 (Heparin)
CN 0 (Indicators and Reagents); 0 (Oligosaccharides)

L6 ANSWER 11 OF 14 MEDLINE
AN 85157497 MEDLINE
DN 85157497
TI Thrombin-inhibitory activity of whale heparin oligosaccharides.
AU Ototani N; Kodama C; Kikuchi M; Yosizawa Z
SO JOURNAL OF BIOCHEMISTRY, (1984 Dec) 96 (6) 1695-703.
Journal code: HIF. ISSN: 0021-924X.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198507
AB Whale heparin was partially digested with a purified heparinase and the oligosaccharide fractions with 8-20 **monosaccharide** units were isolated from the digest by gel filtration on Sephadex G-50, followed by affinity chromatography on a column of **antithrombin III** immobilized on Sepharose 4B. A marked difference in the inhibitory activity for thrombin in the presence of **antithrombin III** was observed between the high-affinity fractions for **antithrombin III** of octasaccharide approximately hexadecasaccharide and those of octadecasaccharide approximately eicosasaccharide. The disaccharide compositions of these hexadeca-, octadeca-, and eicosasaccharides were analyzed by high-performance liquid chromatography after digestion with a mixture of purified heparitinases 1 and 2 and heparinase. The analytical data indicated that the proportions of trisulfated disaccharide (IdUA(2S)alpha 1----4GlcNS(6S)) and disulfated disaccharide (UA1----4GlcNS(6S)) increased with the manifestation of high thrombin-inhibitory activity, while that of monosulfated disaccharide (UA1----4GlcNS) decreased. The present observations, together with those so far reported, suggest that the presence of the former structural elements, specifically IdUA(2S)alpha 1----4GlcNS(6S), as well as the **antithrombin III**-binding pentasaccharide at the proper positions in the molecules of whale heparin oligosaccharides is essential for the manifestation of high inhibitory activity for thrombin in the presence of **antithrombin III**. The structural bases for the manifestation of the anticoagulant activity of whale and porcine heparins and their oligosaccharides are also discussed.
CT Check Tags: Animal; Comparative Study; Support, Non-U.S. Gov't
Antithrombin III: PD, pharmacology
Carbohydrate Sequence
*Cetacea: ME, metabolism
Chromatography, High Pressure Liquid: MT, methods
*Heparin: PD, pharmacology
Hydrolysis
Molecular Weight
Oligosaccharides: IP, isolation & purification
*Oligosaccharides: PD, pharmacology
Polysaccharide-Lyases
Swine
*Thrombin: AI, antagonists & inhibitors
*Whales: ME, metabolism
RN **9000-94-6 (Antithrombin III)**; 9005-49-6 (Heparin)
CN EC 3.4.21.5 (Thrombin); EC 4.2.2. (Polysaccharide-Lyases); EC 4.2.2.7 (Heparin Lyase); 0 (Oligosaccharides)

L6 ANSWER 13 OF 14 MEDLINE
AN 82278007 MEDLINE
DN 82278007
TI Effects of heparin oligosaccharides with high affinity for **antithrombin III** in experimental venous thrombosis.
AU Thomas D P; Merton R E; Barrowcliffe T W; Thunberg L; Lindahl U
SO THROMBOSIS AND HAEMOSTASIS, (1982 Jun 28) 47 (3) 244-8.
Journal code: VQ7. ISSN: 0340-6245.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198212
AB The in vitro and in vivo characteristics of two oligosaccharide heparin fragments have been compared to those of unfractionated mucosal heparin. A decasaccharide fragment had essentially no activity by APTT or calcium thrombin time assays in vitro, but possessed very high specific activity by anti-Factor Xa assays. When injected into rabbits at doses of up to 80 microgram/kg, this fragment was relatively ineffective in impairing stasis thrombosis despite producing high blood levels by anti-Xa assays. A 16-18 **monosaccharide** fragment had even higher specific activity (almost 2000 iu/mg) by chromogenic substrate anti-Xa assay, with minimal activity by APTT. When injected in vivo, this fragment gave low blood levels by APTT, very high anti-Xa levels, and was more effective in preventing thrombosis than the decasaccharide fragment. However, in comparison with unfractionated heparin, the 16-18 **monosaccharide** fragment was only partially effective in preventing thrombosis, despite producing much higher blood levels by anti-Xa assays. It is concluded that the high-affinity binding of a heparin fragment to **antithrombin III** does not by itself impair venous thrombogenesis, and that the anti-Factor Xa activity of heparin is only a partial expression of its therapeutic potential.
CT Check Tags: Animal; Human
***Antithrombin III: ME, metabolism**
Dose-Response Relationship, Drug
Factor X: AI, antagonists & inhibitors
Heparin: BL, blood
*Heparin: TU, therapeutic use
*Oligosaccharides: TU, therapeutic use
Partial Thromboplastin Time
Rabbits
Thrombin Time
Thrombophlebitis: BL, blood
Thrombophlebitis: DI, diagnosis
*Thrombophlebitis: DT, drug therapy
RN **9000-94-6 (Antithrombin III)**; 9001-29-0 (Factor X); 9005-49-6 (Heparin)
CN EC 3.4

L19 ANSWER 1 OF 1 MEDLINE
AN 91218798 MEDLINE
DN 91218798
TI N-acetyl-D-glucosamine is present in cysts and trophozoites of Giardia lamblia and serves as receptor for wheatgerm agglutinin.
AU Ortega-Barria E; Ward H D; Evans J E; Pereira M E
CS Division of Geographic Medicine and Infectious Diseases, New England Medical Center, Tufts University School of Medicine, Boston, MA 02111..
NC AI 121791 (NIAID)
SO MOLECULAR AND BIOCHEMICAL PARASITOLOGY, (1990 Dec) 43 (2) 151-65. Journal code: NOR. ISSN: 0166-6851.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199108
AB Previously, on the basis of lectin binding and glycosidase digestion assays, we have suggested that N-acetyl-D-glucosamine residues (**GlcNAc**) are major structural components of both trophozoites and in vivo cysts of the intestinal parasite Giardia lamblia. In this report we confirm that **GlcNAc** is present both in trophozoites and in vitro cysts as assessed by lectin binding and glycosidase digestion assays, galactosyltransferase labeling, immunochemical analysis using antibodies specific for **GlcNAc** and its beta 1-4 oligomers, and by gas chromatography/mass spectrometry (GC/MS). The results show that wheatgerm agglutinin (WGA) binds specifically to intact trophozoites and in vitro cysts as well as to SDS-PAGE separated proteins. WGA binding to the separated proteins was markedly reduced after their digestion with N-acetyl-beta-D-glucosaminidase, supporting the conclusion that WGA is reacting with terminal beta-linked **GlcNAc** residues. Labeling of trophozoites and cysts by 3H-exogalactosylation with galactosyltransferase further confirmed the presence of terminal **GlcNAc** in both surface and intracellular glycoproteins. The presence of **GlcNAc** is also supported by microfluorometric analysis using antibodies to (**GlcNAc**)1, (**GlcNAc**)2, and (**GlcNAc**)3, which revealed a sugar-inhibitable binding of the antibody to live trophozoites.

Finally, the presence of **GlcNAc** in both cysts and trophozoites was unequivocally confirmed by GC/MS analysis of detergent-extracted membranes and of glycoproteins isolated by affinity chromatography on WGA-agarose. GC/MS analysis also revealed mannose (**Man**), N-acetyl-D-galactosamine (**GalNAc**), fucose (**Fuc**), galactose (**Gal**), glucose (Glc) and N-acetylneuraminic acid (**NANA**) to be present in cysts. All these sugars were also present in trophozoites, except for **GalNAc**. The glycoproteins isolated by WGA affinity chromatography were 5- to 40-fold enriched in **GlcNAc**, further supporting the conclusion that WGA reacts with **GlcNAc** in Giardia. In summary, the data presented here provide biological and chemical evidence for **GlcNAc** in both cysts and trophozoites of G. lamblia and are consistent with previously published results from this and other laboratories.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Acetylglucosamine: AN, analysis
*Acetylglucosamine: ME, metabolism
Cattle
Colostrum: EN, enzymology
Electrophoresis, Polyacrylamide Gel
Galactosyltransferases: ME, metabolism
Giardia: AN, analysis

Giardia: GD, growth & development
*Giardia: ME, metabolism
Immunochemistry
Mass Fragmentography
*Wheat Germ Agglutinins: ME, metabolism
RN 7512-17-6 (Acetylglucosamine)
CN EC 2.4.1.- (Galactosyltransferases)

L46 ANSWER 1 OF 4 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1999:69789 BIOSIS
DN PREV199900069789
TI **Transgenically** produced **antithrombin III**.
AU Ditullio, P.; Meade, H.; Cole, E. S.
CS Framingham, Mass. USA
ASSIGNEE: GENZYME TRANSGENIC CORPORATION
PI US 5843705 Dec. 1, 1998
SO Official Gazette of the United States Patent and Trademark Office Patents,
(Dec. 1, 1998) Vol. 1217, No. 1, pp. 479.
ISSN: 0098-1133.
DT Patent
LA English
NCL 435069001
CC *00100
*04600
*15100
*16200
*21100
*21300
*51200
*51400
*80100
IT Major Concepts
Animal Husbandry (Agriculture); Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); General Life Studies;
Genetics; Miscellaneous Substances; Pharmacology; Reproductive System (Reproduction)
IT Miscellaneous Descriptors
BIOTECHNOLOGY; ENCODING; GOAT **MILK**; HUMAN **ANTITHROMBIN III**; MAMMARY TISSUE; PHARMACEUTICALS; **TRANSGENE** EXPRESSION; **TRANSGENIC** GOAT
ORGN Super Taxa
Mammalia - Unspecified: Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mammal (Mammalia - Unspecified)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; vertebrates

L46 ANSWER 2 OF 4 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:428755 BIOSIS
DN PREV199799727958
TI Therapeutic proteins from the **milk** of **transgenic** livestock: Biosynthesis, purification and safety issues.
AU Velander, William H.
CS Dep. Chem. Engineering, Virginia Tech, Blacksburg, VA 24061 USA
SO Abstracts of Papers American Chemical Society, (1997) Vol. 214, No. 1-2, pp. MEDI 143.
Meeting Info.: 214th American Chemical Society National Meeting Las Vegas,
Nevada, USA September 7-11, 1997
ISSN: 0065-7727.
DT Conference; Abstract
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Cytology and Cytochemistry - Animal *02506

Genetics and Cytogenetics - Animal *03506
Comparative Biochemistry, General *10010
Biochemical Methods - Nucleic Acids, Purines and Pyrimidines *10052
Biochemical Methods - Proteins, Peptides and Amino Acids *10054
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Pathology, General and Miscellaneous - Therapy *12512
Metabolism - Proteins, Peptides and Amino Acids *13012
Blood, Blood-Forming Organs and Body Fluids - Blood and Lymph Studies *15002
Blood, Blood-Forming Organs and Body Fluids - Other Body Fluids *15010
Reproductive System - Physiology and Biochemistry *16504
Endocrine System - General *17002
Pharmacology - General *22002
Animal Production - General; Methods *26502

BC Mammalia - Unspecified 85700
Bovidae 85715
Suidae *85740

IT Major Concepts
Animal Husbandry (Agriculture); Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Genetics; Metabolism; Methods and Techniques; Pathology; Pharmacology; Physiology; Reproductive System (Reproduction)

IT Chemicals & Biochemicals
PROTEIN C; FACTOR VII; **ANTITHROMBIN III**; ALPHA-1-ANTITRYPSIN

IT Miscellaneous Descriptors
ALPHA-1-ANTITRYPSIN; ANIMAL HUSBANDRY; **ANTITHROMBIN III**; BIOSYNTHESIS; BIOTECHNOLOGY; FACTOR IX; FACTOR VII; FIBRINOGEN; GENOTYPE; MAMMARY GLAND; **MILK**; MOLECULAR GENETICS; PHARMACOLOGY; PHENOTYPE; PROTEIN C; PROTEINS; PROTEOLYTIC PROCESSING; PURIFICATION; RECOMBINANT PROTEINS; REPRODUCTIVE SYSTEM; SAFETY; THERAPEUTIC PROTEINS; **TRANSGENIC**

ORGN Super Taxa
Bovidae: Artiodactyla, Mammalia, Vertebrata, Chordata, Animalia; Mammalia - Unspecified: Mammalia, Vertebrata, Chordata, Animalia; Suidae: Artiodactyla, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
goat (Bovidae); livestock (Mammalia - Unspecified); pig (Suidae); sheep (Bovidae); Mammalia (Mammalia - Unspecified)

ORGN Organism Superterms
animals; artiodactyls; chordates; mammals; nonhuman mammals; nonhuman vertebrates; vertebrates

RN 60202-16-6 (PROTEIN C)
9001-25-6 (FACTOR VII)
9000-94-6 (**ANTITHROMBIN III**)
9041-92-3 (ALPHA-1-ANTITRYPSIN)

L46 ANSWER 3 OF 4 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1994:250575 BIOSIS
DN PREV199497263575
TI Tissue specific and species differences in the glycosylation pattern of **antithrombin III**.
AU Edmunds, Tim; Higgins, Elizabeth; Bernasconi, Rick; Garone, Louise; Cole, Edward S.
CS GENZYME Corp., 1 Mountain Road, Framingham, MA 01701-9322 USA
SO Journal of Cellular Biochemistry Supplement, (1994) Vol. 0, No. 18D, pp. 265.
Meeting Info.: Keystone Symposium on Complex Carbohydrates in Biology and Medicine Frisco, Colorado, USA March 19-26, 1994
ISSN: 0733-1959.
DT Conference
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences,

Congresses, Review Annuals 00520
Genetics and Cytogenetics - Animal *03506
Genetics and Cytogenetics - Human *03508
Comparative Biochemistry, General *10010
Biochemical Methods - Carbohydrates 10058
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Carbohydrates *10068
Biophysics - General Biophysical Techniques 10504
Biophysics - Molecular Properties and Macromolecules *10506
Metabolism - Carbohydrates *13004
Metabolism - Proteins, Peptides and Amino Acids *13012
Blood, Blood-Forming Organs and Body Fluids - Blood and Lymph Studies *15002
Reproductive System - Physiology and Biochemistry *16504
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508

BC Bovidae 85715
Hominidae *86215

IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Clinical Immunology (Human Medicine, Medical Sciences); Genetics; Metabolism; Reproductive System (Reproduction)

IT Chemicals & Biochemicals
ANTITHROMBIN III

IT Miscellaneous Descriptors
FLUOROPHORE ASSISTED CARBOHYDRATE ANALYSIS; MEETING ABSTRACT; MEETING POSTER; **MILK**; **TRANSGENIC** GOATS

ORGN Super Taxa
Bovidae: Artiodactyla, Mammalia, Vertebrata, Chordata, Animalia; Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae); Bovidae (Bovidae)

ORGN Organism Superterms
animals; artiodactyls; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; vertebrates

RN 9000-94-6 (**ANTITHROMBIN III**)

L46 ANSWER 4 OF 4 BIOSIS COPYRIGHT 1999 BIOSIS

AN 1994:250573 BIOSIS

DN PREV199497263573

TI Glycosylation patterns of human proteins expressed in **transgenic** goat **milk**.

AU Cole, Edward S.; Higgins, Elizabeth; Bernasconi, Rick; Garone, Louise; Edmunds, Tim

CS GENZYME Corp., 1 Mountain Road, Framingham, MA 01701-9322 USA

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Genetics and Cytogenetics - Animal *03506
Genetics and Cytogenetics - Human *03508
Comparative Biochemistry, General *10010
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Carbohydrates *10068
Replication, Transcription, Translation 10300
Biophysics - General Biophysical Techniques 10504
Biophysics - Molecular Properties and Macromolecules *10506
Metabolism - Carbohydrates *13004
Metabolism - Proteins, Peptides and Amino Acids *13012
Blood, Blood-Forming Organs and Body Fluids - Other Body Fluids *15010

Reproductive System - Physiology and Biochemistry *16504
BC Bovidae 85715
Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Genetics; Metabolism; Physiology; Reproductive System (Reproduction)
IT Chemicals & Biochemicals
N-ACETYLNEURAMINIC ACID; **ANTITHROMBIN-III**
IT Miscellaneous Descriptors
ANTITHROMBIN-III, TISSUE PLASMINOGEN ACTIVATOR; COMPLEX CARBOHYDRATES; ELECTROSPRAY MASS SPECTROMETRY; FLUOROPHORE ASSISTED CARBOHYDRATE ELECTROPHORESIS; MEETING ABSTRACT; MEETING POSTER; N-ACETYLNEURAMINIC ACID; N-GLYCOLYLNEURAMINIC ACID
ORGN Super Taxa
Bovidae: Artiodactyla, Mammalia, Vertebrata, Chordata, Animalia; Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Bovidae (Bovidae); Hominidae (Hominidae)
ORGN Organism Superterms
animals; artiodactyls; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; vertebrates
RN 131-48-6 (N-ACETYLNEURAMINIC ACID)
9000-94-6 (**ANTITHROMBIN-III**)

L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 1999 ACS
AN 1997:343782 CAPLUS
DN 127:61135
TI Adrenomedullin as an autocrine/paracrine apoptosis survival factor for rat endothelial cells
AU Kato, Hiroki; Shichiri, Masayoshi; Marumo, Fumiaki; Hirata, Yukio
CS Endocrine-Hypertension Division, Second Department of Internal Medicine, Tokyo Medical and Dental University, Tokyo, 113, Japan
SO Endocrinology (1997), 138(6), 2615-2620
CODEN: ENDOAO; ISSN: 0013-7227
PB Endocrine Society
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB Adrenomedullin is a potent vasorelaxant/hypotensive peptide recently isolated from human pheochromocytoma. We demonstrate here a novel role of this peptide as an apoptosis survival factor for rat endothelial cells. When rendered quiescent by serum deprivation, a fraction of endothelial cell cultures showed morphol. and biochem. features characteristic of apoptosis. Adrenomedullin significantly suppressed apoptosis without inducing cell proliferation. Rat endothelial cells that contained **high affinity binding** sites for adrenomedullin expressed adrenomedullin **gene** and released the peptide into culture media. Addn. of preimmune rabbit serum prevented apoptosis, whereas rabbit antiadrenomedullin antiserum partially, but significantly, abrogated the protective effect of the preimmune serum, suggesting its autocrine/paracrine role. Although adrenomedullin induced intracellular cAMP formation, other cAMP-elevating agonists, such as prostaglandin I2 and forskolin, did not affect apoptosis. Furthermore, adenosine 3',5'-cyclic monophosphothioate Rp-isomer, a cAMP antagonist, did not block the cell survival effect of adrenomedullin. Adrenomedullin neither increased intracellular Ca2+ concns. nor **inositol-1, 4,5-trisphosphate** levels in rat endothelial cells. These results demonstrate that adrenomedullin suppresses serum deprivation-induced apoptosis of rat endothelial cells via cAMP-independent mechanism.
ST adrenomedullin apoptosis **vascular** endothelium cAMP
IT Apoptosis
Calcium transport (biological)
Cell proliferation
Second messenger system
Serum (blood)
Vascular endothelium
(adrenomedullin suppresses serum deprivation-induced apoptosis of endothelial cells via cAMP-independent mechanism)
IT Genes (animal)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(adrenomedullin suppresses serum deprivation-induced apoptosis of endothelial cells via cAMP-independent mechanism)
IT Hormone receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(adrenomedullin; adrenomedullin suppresses serum deprivation-induced apoptosis of endothelial cells via cAMP-independent mechanism)
IT 154835-90-2, Adrenomedullin
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(adrenomedullin suppresses serum deprivation-induced apoptosis of endothelial cells via cAMP-independent mechanism)

IT 60-92-4, CAMP
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(adrenomedullin suppresses serum deprivation-induced apoptosis of endothelial cells via cAMP-independent mechanism)

IT 7440-70-2, Calcium, biological studies 88269-39-0, **Inositol-1,4,5-trisphosphate**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(adrenomedullin suppresses serum deprivation-induced apoptosis of endothelial cells via cAMP-independent mechanism)

6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 1999 ACS
AN 1999:343182 CAPLUS
DN 131:140289
TI Molecular cloning of the mouse follicle-stimulating hormone receptor complementary deoxyribonucleic acid: functional expression of alternatively spliced variants and receptor inactivation by a C566T transition in Exon 7 of the coding sequence
AU Tena-Sempere, Manuel; Manna, Pulak R.; Huhtaniemi, Ilpo
CS Department of Physiology, University of Turku, Turku, 20520, Finland
SO Biol. Reprod. (1999), 60(6), 1515-1527
CODEN: BIREBV; ISSN: 0006-3363
PB Society for the Study of Reproduction
DT Journal
LA English
CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 2, 14
AB The gonadotropin receptors, i.e., those of LH and FSH (FSHR), are pivotal elements in the regulation of gonadal function. Recently, extensive efforts have been made to elucidate the structure-function relation of these receptors as well as the modulatory mechanism(s) of their function. In the present study, the authors report (1) characterization of the mouse (m) FSHR cDNA coding sequence and (2) the functional consequences of coexpression of several splice variants of the mFSHR. In addn., the authors evaluate (3) the impact on mFSHR function of a C566T transition in exon 7 of the coding sequence, a substitution analogous to the inactivating mutation in the human FSHR **gene** responsible for a hereditary form of hypergonadotropic ovarian failure. Mol. cloning of the mFSHR cDNA was carried out by reverse transcription-polymerase chain reaction (RT-PCR) using 129/Sv mouse testicular RNA and primers complementary to the rat or the partially characterized mouse FSHR sequence. Overlapping partial fragments of receptor cDNA were amplified, sequenced, and engineered to produce the entire cDNA coding sequence, subcloned into the pSG5 expression vector. Using a similar approach, 4 different receptor splice variants, selectively lacking exons 2, 2 and 5, 5 and 6, and 2, 5, and 6 of the coding region, were cloned. Finally, PCR-based site-directed mutagenesis was used to generate the C566T mutant of mFSHR. Sequence anal. showed an open reading frame of 2076 base pairs for the mFSHR cDNA, predicting a putative 17-amino acid signal peptide and a 675-amino acid mature receptor protein, and overall sequence homol. of 94% with rat, 87% with human, and 85-84% with bovine, and ovine FSHRs. Functional expression in human embryonic kidney (HEK 293) and mouse granulosa (KK-1) cells demonstrated for the cloned receptor **high -affinity binding** to recombinant human (rh) FSH and ability to elicit cAMP, **inositol** trisphosphate (IP3), and progesterone responses. In contrast, transient transfection studies showed that despite successful transcription, the exon-lacking FSHR variants were unable to bind rhFSH either in intact or in solubilized HEK 293 cells, or to elicit cAMP or progesterone responses in KK-1 cells. Furthermore, cotransfections of the splice variants in the context of an ovarian cell line stably expressing the full-length mFSHR failed to demonstrate modulatory effects on the holoreceptor function. Finally, transient expression of the C566T mFSHR mutant in HEK 293 cells revealed that, in accordance with observations on human FSHR, this substitution profoundly impaired the ligand binding and cAMP and IP3 responses to rhFSH stimulation. In conclusion, the present data indicate that, despite

extensive splicing of the mFSHR message, a potential role of the exon-lacking receptor transcripts in modulating FSH actions is unlikely. In addn., the authors provide evidence for mFSHR inactivation by a C566T transition in exon 7 of the coding sequence, thus paving the way for further development of animal models of hypergonadotropic ovarian failure.

ST mouse FSH receptor cDNA sequence expression hypergonadotropic ovarian failure; **gene** FSH receptor mutation hypergonadotropic ovarian failure; splicing variant FSH receptor expression

IT Genes (animal)
RL: BOC (Biological occurrence); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(Fshr; sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by hypergonadotropic ovarian failure-assocd. C566T transition in exon 7 of coding sequence)

IT Ovarian **diseases**
(failure, hypergonadotropic; sequence of mouse FSH receptor cDNA, expression of spliced variants in human and mouse cells and receptor inactivation by hypergonadotropic ovarian failure-assocd. C566T transition in exon 7 of coding sequence)

IT Protein sequences
(homol.; protein sequence homol. of mouse FSH receptor with other mammalian FSH receptors)

IT Splicing (RNA)
(messenger; sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by C566T transition in exon 7 of coding sequence)

IT **Disease** models
Gene expression
Mouse (Mus musculus)
Protein sequences
Transcription (genetic)
Transition mutation
cDNA sequences
(sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by hypergonadotropic ovarian failure-assocd. C566T transition in exon 7 of coding sequence)

IT Exon (genetic element)
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence);
PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by hypergonadotropic ovarian failure-assocd. C566T transition in exon 7 of coding sequence)

IT mRNA
RL: BOC (Biological occurrence); BPR (Biological process); MFM (Metabolic formation); PRP (Properties); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PROC (Process)
(sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by hypergonadotropic ovarian failure-assocd. C566T transition in exon 7 of coding sequence)

IT FSH receptors
RL: BOC (Biological occurrence); BPR (Biological process); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by hypergonadotropic ovarian failure-assocd. C566T transition in exon 7 of coding sequence)

IT Pre-mRNA
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(splicing; sequence of mouse FSH receptor cDNA, functional expression

of alternatively spliced variants in human and mouse cells and receptor
inactivation by C566T transition in exon 7 of coding sequence)
IT 57-83-0, Progesterone, biological studies 60-92-4, CAMP 85166-31-0, D-myo-**Inositol 1,4,5-trisphosphate**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(FSH-induced response; sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by C566T transition in exon 7 of coding sequence)
IT 234764-60-4
RL: PRP (Properties)
(amino acid sequence; sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by C566T transition in exon 7 of coding sequence)
IT 218721-47-2, GenBank AF095642
RL: PRP (Properties)
(nucleotide sequence; sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by C566T transition in exon 7 of coding sequence)
IT 9002-68-0, FSH
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by hypergonadotropic ovarian failure-assocd. C566T transition in exon 7 of coding sequence)

L5 ANSWER 1 OF 8 CAPLUS COPYRIGHT 1999 ACS
AN 1999:537292 CAPLUS
DN 131:346963
TI Free-radical-generated F2-isoprostane stimulates cell proliferation and endothelin-1 expression on endothelial cells
AU Yura, Takafumi; Fukunaga, Megumu; Khan, Rizwan; Nassar, George N.; Badr, Kamal F.; Montero, Angel
CS Renal Division, Department of Medicine, Emory University and Veterans Affairs Medical Center, Atlanta, GA, USA
SO Kidney Int. (1999), 56(2), 471-478
CODEN: KDYIA5; ISSN: 0085-2538
PB Blackwell Science, Inc.
DT Journal
LA English
CC 2-9 (Mammalian Hormones)
AB Free-radical-generated F2-isoprostane stimulates DNA synthesis and endothelin-1 (ET-1) expression on endothelial cells. 8-Iso-prostaglandin F2.alpha. (8-iso-PGF2.alpha.) is a member of the recently discovered family of prostanoids, the F2-isoprostanes, produced in vivo by cyclooxygenase-independent, free-radical-catalyzed lipid peroxidn. The goal of the authors' study is to establish the effect of isoprostane on ET-1 prodn. by endothelial cells, as well to det. the receptors responsible for these effects. The proliferative effect of isoprostanes was measured as an increase of viable cell no. and [3H]-thymidine uptake. ET-1 **gene** expression and protein synthesis were detd. by Northern blot and RIA, resp. The authors also detd. **inositol 1,4,5-trisphosphate** synthesis. Thromboxane A2 (TXA2) receptor antagonist SQ29,548 was used to establish the role of TXA2 receptor in isoprostane effect, as well as to det. the type of receptors involved in these effects. The authors' results show that physiol. concns. of 8-iso-PGF2.alpha. stimulated cell proliferation, DNA synthesis, and ET-1 mRNA and protein expression in bovine aortic endothelial cells (BAECs). The proliferative effect was partially abolished by treatment with anti-endothelin antibody. 8-Iso-PGF2.alpha. also increased **inositol 1,4,5-trisphosphate** formation in these cells. These effects were partially inhibited by SQ29,548. In competitive binding assays, two binding sites were recognized on BAECs with dissocn. consts. (Kd) and binding site densities at equil. similar to those previously described in smooth muscle cells and likely represent [3H]-8-iso-PGF2.alpha. binding to its own receptor (**high-affinity binding** site) and cross-recognition of the TXA2 receptor (low-affinity binding site). These studies expand the potential scope of the pathophysiol. significance of F2-isoprostanes, released during oxidant injury, to include alteration of endothelial cell biol.
ST PGF 2alpha ET1 expression proliferation endothelium signaling free radical
IT Artery
(aorta, endothelium, bovine; free radical generated F2-isoprostane stimulates cell proliferation and endothelin-1 expression on endothelial cells)
IT Cell proliferation
Radical ions
Second messenger system
Tobacco smoke
Transcriptional regulation
(free radical generated F2-isoprostane stimulates cell proliferation and endothelin-1 expression on endothelial cells)
IT Thromboxane receptors

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(free radical generated F2-isoprostane stimulates cell proliferation and endothelin-1 expression on endothelial cells)

IT Phosphoinositides
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(free radical generated F2-isoprostane stimulates cell proliferation and endothelin-1 expression on endothelial cells)

IT 27415-26-5, 8-Iso-prostaglandin F2.alpha.
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(free radical generated F2-isoprostane stimulates cell proliferation and endothelin-1 expression on endothelial cells)

IT 123626-67-5, Endothelin-1
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(free radical generated F2-isoprostane stimulates cell proliferation and endothelin-1 expression on endothelial cells)

IT 88269-39-0, **Inositol-1,4,5-trisphosphate**
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(free radical generated F2-isoprostane stimulates cell proliferation and endothelin-1 expression on endothelial cells)

L5 ANSWER 2 OF 8 CAPLUS COPYRIGHT 1999 ACS
AN 1999:343182 CAPLUS
DN 131:140289
TI Molecular cloning of the mouse follicle-stimulating hormone receptor complementary deoxyribonucleic acid: functional expression of alternatively spliced variants and receptor inactivation by a C566T transition in Exon 7 of the coding sequence
AU Tena-Sempere, Manuel; Manna, Pulak R.; Huhtaniemi, Ilpo
CS Department of Physiology, University of Turku, Turku, 20520, Finland
SO Biol. Reprod. (1999), 60(6), 1515-1527
CODEN: BIREBV; ISSN: 0006-3363
PB Society for the Study of Reproduction
DT Journal
LA English
CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 2, 14
AB The gonadotropin receptors, i.e., those of LH and FSH (FSHR), are pivotal elements in the regulation of gonadal function. Recently, extensive efforts have been made to elucidate the structure-function relation of these receptors as well as the modulatory mechanism(s) of their function. In the present study, the authors report (1) characterization of the mouse (m) FSHR cDNA coding sequence and (2) the functional consequences of coexpression of several splice variants of the mFSHR. In addn., the authors evaluate (3) the impact on mFSHR function of a C566T transition in exon 7 of the coding sequence, a substitution analogous to the inactivating mutation in the human FSHR **gene** responsible for a hereditary form of hypergonadotropic ovarian failure. Mol. cloning of the mFSHR cDNA was carried out by reverse transcription-polymerase chain reaction (RT-PCR) using 129/Sv mouse testicular RNA and primers complementary to the rat or the partially characterized mouse FSHR sequence. Overlapping partial fragments of receptor cDNA were amplified, sequenced, and engineered to produce the entire cDNA coding sequence, subcloned into the pSG5 expression vector. Using a similar approach, 4 different receptor splice variants, selectively lacking exons 2, 2 and 5, 5 and 6, and 2, 5, and 6 of the coding region, were cloned. Finally, PCR-based site-directed mutagenesis was used to generate the C566T mutant of mFSHR. Sequence anal. showed an open reading frame of 2076 base pairs for the mFSHR cDNA, predicting a putative 17-amino acid signal peptide and

a 675-amino acid mature receptor protein, and overall sequence homol. of 94% with rat, 87% with human, and 85-84% with bovine, and ovine FSHRs. Functional expression in human embryonic kidney (HEK 293) and mouse granulosa (KK-1) cells demonstrated for the cloned receptor **high -affinity binding** to recombinant human (rh) FSH and ability to elicit cAMP, **inositol** trisphosphate (IP3), and progesterone responses. In contrast, transient transfection studies showed that despite successful transcription, the exon-lacking FSHR variants were unable to bind rhFSH either in intact or in solubilized HEK 293 cells, or to elicit cAMP or progesterone responses in KK-1 cells. Furthermore, cotransfections of the splice variants in the context of an ovarian cell line stably expressing the full-length mFSHR failed to demonstrate modulatory effects on the holoreceptor function. Finally, transient expression of the C566T mFSHR mutant in HEK 293 cells revealed that, in accordance with observations on human FSHR, this substitution profoundly impaired the ligand binding and cAMP and IP3 responses to rhFSH stimulation. In conclusion, the present data indicate that, despite extensive splicing of the mFSHR message, a potential role of the exon-lacking receptor transcripts in modulating FSH actions is unlikely. In addn., the authors provide evidence for mFSHR inactivation by a C566T transition in exon 7 of the coding sequence, thus paving the way for further development of animal models of hypergonadotropic ovarian failure.

ST mouse FSH receptor cDNA sequence expression hypergonadotropic ovarian failure; **gene** FSH receptor mutation hypergonadotropic ovarian failure; splicing variant FSH receptor expression

IT Genes (animal)
RL: BOC (Biological occurrence); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(Fshr; sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by hypergonadotropic ovarian failure-assocd. C566T transition in exon 7 of coding sequence)

IT Ovarian diseases
(failure, hypergonadotropic; sequence of mouse FSH receptor cDNA, expression of spliced variants in human and mouse cells and receptor inactivation by hypergonadotropic ovarian failure-assocd. C566T transition in exon 7 of coding sequence)

IT Protein sequences
(homol.; protein sequence homol. of mouse FSH receptor with other mammalian FSH receptors)

IT Splicing (RNA)
(messenger; sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by C566T transition in exon 7 of coding sequence)

IT Disease models
Gene expression
Mouse (Mus musculus)
Protein sequences
Transcription (genetic)
Transition mutation
cDNA sequences
(sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by hypergonadotropic ovarian failure-assocd. C566T transition in exon 7 of coding sequence)

IT Exon (genetic element)
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence);
PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by hypergonadotropic ovarian failure-assocd. C566T transition in exon 7 of coding sequence)

IT mRNA
RL: BOC (Biological occurrence); BPR (Biological process); MFM (Metabolic formation); PRP (Properties); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PROC (Process)
(sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by hypergonadotropic ovarian failure-assocd. C566T transition in exon 7 of coding sequence)
IT FSH receptors
RL: BOC (Biological occurrence); BPR (Biological process); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by hypergonadotropic ovarian failure-assocd. C566T transition in exon 7 of coding sequence)
IT Pre-mRNA
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(splicing; sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor
inactivation by C566T transition in exon 7 of coding sequence)
IT 57-83-0, Progesterone, biological studies 60-92-4, CAMP 85166-31-0, D-myo-**Inositol 1,4,5-trisphosphate**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(FSH-induced response; sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by C566T transition in exon 7 of coding sequence)
IT 234764-60-4
RL: PRP (Properties)
(amino acid sequence; sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by C566T transition in exon 7 of coding sequence)
IT 218721-47-2, GenBank AF095642
RL: PRP (Properties)
(nucleotide sequence; sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by C566T transition in exon 7 of coding sequence)
IT 9002-68-0, FSH
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(sequence of mouse FSH receptor cDNA, functional expression of alternatively spliced variants in human and mouse cells and receptor inactivation by hypergonadotropic ovarian failure-assocd. C566T transition in exon 7 of coding sequence)

L5 ANSWER 3 OF 8 CAPLUS COPYRIGHT 1999 ACS
AN 1997:343782 CAPLUS
DN 127:61135
TI Adrenomedullin as an autocrine/paracrine apoptosis survival factor for rat endothelial cells
AU Kato, Hiroki; Shichiri, Masayoshi; Marumo, Fumiaki; Hirata, Yukio
CS Endocrine-Hypertension Division, Second Department of Internal Medicine, Tokyo Medical and Dental University, Tokyo, 113, Japan
SO Endocrinology (1997), 138(6), 2615-2620
CODEN: ENDOAO; ISSN: 0013-7227
PB Endocrine Society
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB Adrenomedullin is a potent vasorelaxant/hypotensive peptide recently

isolated from human pheochromocytoma. We demonstrate here a novel role of this peptide as an apoptosis survival factor for rat endothelial cells. When rendered quiescent by serum deprivation, a fraction of endothelial cell cultures showed morphol. and biochem. features characteristic of apoptosis. Adrenomedullin significantly suppressed apoptosis without inducing cell proliferation. Rat endothelial cells that contained **high affinity binding** sites for adrenomedullin expressed adrenomedullin **gene** and released the peptide into culture media. Addn. of preimmune rabbit serum prevented apoptosis, whereas rabbit antiadrenomedullin antiserum partially, but significantly, abrogated the protective effect of the preimmune serum, suggesting its autocrine/paracrine role. Although adrenomedullin induced intracellular cAMP formation, other cAMP-elevating agonists, such as prostaglandin I2 and forskolin, did not affect apoptosis. Furthermore, adenosine 3',5'-cyclic monophosphothioate Rp-isomer, a cAMP antagonist, did not block the cell survival effect of adrenomedullin. Adrenomedullin neither increased intracellular Ca2+ concns. nor **inositol-1, 4,5-trisphosphate** levels in rat endothelial cells. These results demonstrate that adrenomedullin suppresses serum deprivation-induced apoptosis of rat endothelial cells via cAMP-independent mechanism.

ST adrenomedullin apoptosis vascular endothelium cAMP

IT Apoptosis
Calcium transport (biological)
Cell proliferation
Second messenger system
Serum (blood)
Vascular endothelium
(adrenomedullin suppresses serum deprivation-induced apoptosis of endothelial cells via cAMP-independent mechanism)

IT Genes (animal)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(adrenomedullin suppresses serum deprivation-induced apoptosis of endothelial cells via cAMP-independent mechanism)

IT Hormone receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(adrenomedullin; adrenomedullin suppresses serum deprivation-induced apoptosis of endothelial cells via cAMP-independent mechanism)

IT 154835-90-2, Adrenomedullin
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(adrenomedullin suppresses serum deprivation-induced apoptosis of endothelial cells via cAMP-independent mechanism)

IT 60-92-4, CAMP
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(adrenomedullin suppresses serum deprivation-induced apoptosis of endothelial cells via cAMP-independent mechanism)

IT 7440-70-2, Calcium, biological studies 88269-39-0, **Inositol-1,4,5-trisphosphate**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(adrenomedullin suppresses serum deprivation-induced apoptosis of endothelial cells via cAMP-independent mechanism)

L5 ANSWER 4 OF 8 CAPLUS COPYRIGHT 1999 ACS
AN 1995:767118 CAPLUS
DN 124:22062
TI Selection and characterization of mammalian cell lines with stable over-expression of human pituitary receptors for gonadoliberin
AU Beckers, Thomas; Marheineke, Kathrin; Reilaender, Helmut; Hilgard, Peter
CS ASTA Medica AG, Frankfurt/Main, Germany
SO Eur. J. Biochem. (1995), 231(3), 535-43
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal

LA English
CC 2-5 (Mammalian Hormones)
AB The cDNA encoding the receptor for gonadoliberin (GnRH or LH-RH) was isolated from a human pituitary cDNA library and heterologously expressed in the murine fibroblast cell line LTK-. By using a dicistronic expression strategy utilizing the internal ribosomal-entry-site sequence of poliovirus, single cell clones with stable and high expression of human gonadoliberin receptors were selected. The gonadoliberin antagonist Cetrorelix showed **high-affinity binding** to the heterologously expressed human gonadoliberin receptor with a Kd of 0.1 nM in radioligand satn.-binding expts. The pharmacol. profile using 125I-Cetrorelix as radioligand and the authentic gonadoliberin or agonistic and antagonistic derivs. as competitors, showed a distinct rank order of binding potencies. Superagonistic gonadoliberin derivs. had more than 10 times higher binding affinities in comparison to gonadoliberin with a Kd of 3.47 nM. The gonadoliberin receptor expressed in stably transfected LTK- cells coupled to the **inositol** phosphate signal-transduction pathway. Gonadoliberin stimulated the synthesis of **inositol 1,4,5-trisphosphate** in a dose-dependent way with an EC50 of 5 nM. This stimulatory effect of gonadoliberin was completely antagonized by Cetrorelix in equimolar concns., demonstrating the high potency of this competitive receptor antagonist. A transient expression of the c-fos protooncogene in growth-arrested cells was induced by gonadoliberin or [D-Trp6]gonadoliberin. The gonadoliberin receptor couples to a putative mitogenic signal-transduction pathway in this heterologous cell system.
ST gonadoliberin receptor cDNA cloning cell line; LHRH receptor characterization fibroblast cell line
IT Signal transduction, biological
(gonadoliberin receptors function and characterization after stable over-expression in fibroblast cell line)
IT Receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(LH-releasing factor, gonadoliberin receptors function and characterization after stable over-expression in fibroblast cell line)
IT Animal cell line
(LTK-, gonadoliberin receptors function and characterization after stable over-expression in fibroblast cell line)
IT **Gene**, animal
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(c-fos, gonadoliberin receptors function and characterization after stable over-expression in fibroblast cell line)
IT 52435-06-0 57773-63-4 57982-77-1 112568-12-4, Antide 120287-85-6, Cetrorelix 151272-78-5, Antarelix
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(gonadoliberin receptors function and characterization after stable over-expression in fibroblast cell line)
IT 9034-40-6, LH-RH
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gonadoliberin receptors function and characterization after stable over-expression in fibroblast cell line)
IT 88269-39-0, **Inositol 1,4,5-trisphosphate**
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(gonadoliberin receptors function and characterization after stable over-expression in fibroblast cell line)

L5 ANSWER 5 OF 8 CAPLUS COPYRIGHT 1999 ACS
AN 1995:358243 CAPLUS
DN 122:181931
TI src-Homology 2 (SH2) domain ligation as an allosteric regulator:

modulation of phosphoinositide-specific phospholipase C.gamma.1 structure and activity

AU Koblan, Kenneth S.; Schaber, Michael D.; Edwards, Gwynneth; Gibbs, Jackson B.; Pompliano, David L.

CS Dep. Cancer Res., Merck Res. Lab., West Point, PA, 19486, USA

SO Biochem. J. (1995), 305(3), 745-51
CODEN: BIJOAK; ISSN: 0264-6021

DT Journal

LA English

CC 7-5 (Enzymes)
Section cross-reference(s): 3

AB Phosphatidylinositol (PI)-specific phospholipase C.gamma.1 (PI-PLC.gamma.1) catalyzes the hydrolysis of PI 4,5-bisphosphate (PIP2) to generate the 2nd messengers diacylglycerol and **inositol 1,4,5-trisphosphate**. PI-PLC.gamma.1, an src-homol. 2/3 (SH2/SH3) domain-contg. enzyme, is activated in response to growth factor-induced tyrosine phosphorylation, and, in vivo, is translocated from the cytosol to the particulate cell fraction. Here, the authors report the bacterial (Escherichia coli) expression of rat brain PI-PLC.gamma.1 under the control of the phage T7 promoter. Prodn. of the active enzyme in amts. suitable for structure-function anal. depended on coupling the translation of PI-PLC.gamma.1 to the expression of the phage-.vphi.10 coat protein. Purifn. of the enzyme was facilitated by the presence of a 3-amino-acid C-terminal antibody epitope tag (Glu-Glu-Phe) engineered into the cloned PI-PLC.gamma.1. Examn. of the specific activity, pH-rate profile, [Ca2+]-dependence, and substrate specificity of bacterially expressed PI-PLC.gamma. indicated that it had kinetic properties similar to those of PI-PLC.gamma. isolated from bovine brain. The substrate specificity was dependent on [Ca2+]: at low [Ca2+] (1-10 .mu.M), PIP2 was a better substrate than PI. The addn. of phosphotyrosine-contg. peptides (12-mers) with the cognate sequence of the **high-affinity binding** site for PI-PLC.gamma.1 on the activated epidermal growth factor (EGF) receptor (Tyr-992) increased enzyme activity (up to 85%) in vitro. Cognate nonphosphorylated peptides had no effect on enzyme activity. When CD spectroscopy was used to monitor the effect of added phosphotyrosine-contg. peptide on the structure of recombinant PI-PLC.gamma.1, significant spectral shifts, indicative of a conformational change, were obsd. upon complexation with the EGF-receptor phosphotyrosine-contg. 12-residue peptide (Tyr*-992). How SH2 domains from PI-PLC.gamma.1 can mediate structural rearrangements and modulate enzymic activity on their ligation by growth factor receptors was discussed.

ST phosphinositide phospholipase C recombinant form brain; conformation change recombinant phosphinositide phospholipase C; Escherichia expression rat brain phospholipase C

IT Escherichia coli
(cloning and expression of rat brain phosphatidylinositol phospholipase C in Escherichia coli)

IT Conformation and Conformers
(modulation of recombinant rat brain phosphoinositide-specific phospholipase C.gamma.1 structure by phosphotyrosine-contg. phosphopeptides)

IT Brain
(src-homol. 2 (SH2) domain ligation as an allosteric regulator: modulation of recombinant rat brain phosphoinositide-specific phospholipase C.gamma.1 structure and activity)

IT Receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(epidermal growth factor/.alpha.-transforming growth factor,

gene c-erbB, src-homol. 2 (SH2) domain ligation as an allosteric regulator: modulation of recombinant rat brain phosphoinositide-specific phospholipase C.gamma.1 structure and activity)

IT Phosphopeptides
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(phosphotyrosine-contg., modulation of recombinant rat brain phosphoinositide-specific phospholipase C.gamma.1 structure by phosphotyrosine-contg. phosphopeptides)

IT Animal growth regulator receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(.alpha.-transforming growth factor **gene** c-erbB, src-homol. 2 (SH2) domain ligation as an allosteric regulator: modulation of recombinant rat brain phosphoinositide-specific phospholipase C.gamma.1
structure and activity)

IT 63551-76-8P, Phosphatidylinositol phospholipase C
RL: BPN (Biosynthetic preparation); PEP (Physical, engineering or chemical
process); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); PROC (Process)
(isoform .gamma.1; src-homol. 2 (SH2) domain ligation as an allosteric regulator: modulation of recombinant rat brain phosphoinositide-specific phospholipase C.gamma.1 structure and activity)

L5 ANSWER 6 OF 8 CAPLUS COPYRIGHT 1999 ACS
AN 1993:18143 CAPLUS
DN 118:18143
TI Structure of a novel InsP3 receptor
AU Sudhof, Thomas C.; Newton, Christopher L.; Archer, Branch T., III; Ushkaryov, Yuri A.; Mignery, Gregory A.
CS Southwest. Med. Cent., Univ. Texas, Dallas, TX, 75235, USA
SO EMBO J. (1991), 10(11), 3199-206
CODEN: EMJODG; ISSN: 0261-4189
DT Journal
LA English
CC 6-3 (General Biochemistry)
Section cross-reference(s): 2, 3, 13
AB **Inositol 1,4,5-trisphosphate** (InsP3) constitutes a major intracellular second messenger that transduces many growth factor and neurotransmitter signals.
InsP3 causes the release of Ca2+ from intracellular stores by binding to specific receptors that are coupled to Ca2+ channels. One such receptor from cerebellum has previously been extensively characterized. The authors have now detd. the full structure of a second, novel InsP3 receptor which is referred to as type 2 InsP3 receptor as opposed to the cerebellar type 1 InsP3 receptor. The type 2 InsP3 receptor has the same general structural design as the cerebellar type 1 InsP3 receptor with which it shares 69% sequence identity. Expression of the N-terminal 1078 amino acids of the type 2 receptor demonstrates **high-affinity binding** of InsP3 to the type 2 receptor with a similar specificity but higher affinity than obsd. for the type I receptor. These results demonstrate the presence of several types of InsP3 receptor in brain and raise the possibility that intracellular Ca2+ signaling may involve multiple pathways with different regulatory properties dependent on different InsP3 receptors.
ST rat **inositol** trisphosphate receptor **gene**; **inositol** trisphosphate receptor sequence cerebellum; protein **inositol** trisphosphate binding cerebellum
IT **Gene**, animal
RL: BIOL (Biological study)
(for **inositol** tris(phosphate)receptor type 2, of rat cerebellum, nucleotide sequence of)
IT Rat
(**inositol** tris(phosphate) receptor type 2 **gene** of

cerebellum of, nucleotide sequence of)
IT Deoxyribonucleic acid sequences
(**inositol** tris(phosphate)-binding protein-specifying, type 2, of cerebellum, of rat, complete)
IT Protein sequences
(of **inositol** tris(phosphate) receptor type II, of rat cerebellum, complete)
IT Brain, composition
(cerebellum, **inositol** tris(phosphate) receptor type 2 of, amino acid sequence of)
IT Receptors
RL: BIOL (Biological study)
(**inositol** tris(phosphate), type 2, amino acid sequence of, of cerebellum)
IT Proteins, specific or class
RL: BIOL (Biological study)
(**inositol** tris(phosphate)-binding, type 2, amino acid sequence of, of cerebellum)
IT 145112-31-8, Protein (rat clone p547-13/pI71/pI70/pI53/pI15/pI6 **inositol** tris(phosphate)-binding isoform 2 reduced)
RL: PRP (Properties)
(amino acid sequence of)
IT 140991-42-0 145112-30-7
RL: PRP (Properties)
(nucleotide sequence of)
IT 88269-39-0, **Inositol 1,4,5-trisphosphate**
RL: BIOL (Biological study)
(receptor for, type 2, amino acid sequence of, of cerebellum of rat)

L5 ANSWER 7 OF 8 CAPLUS COPYRIGHT 1999 ACS
AN 1992:100352 CAPLUS
DN 116:100352
TI Cloning and expression of a complementary DNA encoding a bovine adrenal angiotensin II type-1 receptor
AU Sasaki, Katsutoshi; Yamano, Yoshiaki; Bardhan, Smriti; Iwai, Naoharu; Murray, John J.; Hasegawa, Mamoru; Matsuda, Yuzuru; Inagami, Tadashi
CS Dep. Biochem., Vanderbilt Univ., Nashville, TN, 37232, USA
SO Nature (London) (1991), 351(6323), 230-3
CODEN: NATUAS; ISSN: 0028-0836
DT Journal
LA English
CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 6, 13
AB The expression cloning of a cDNA encoding a bovine angiotensin II receptor is reported. The receptor cDNA encodes a protein of 359 amino-acid residues with a transmembrane topol. similar to that of other G protein-coupled receptors. COS-7 cells transfected with the cDNA expressed specific and **high-affinity binding** sites for angiotensin II, angiotensin II antagonist and a non-peptide specific antagonist for type-1 receptor. Dithiothreitol inhibited ligand binding. The concn. of intracellular Ca2+ and of **inositol-1,4,5-trisphosphate** increased in the transfected COS-7 cells in response to angiotensin II or angiotensin III, indicating that this receptor is the type-1 receptor for angiotensin II. Northern blot anal. revealed that the mRNA for this receptor is expressed in bovine adrenal medulla, cortex and kidney.
ST cattle angiotensin receptor cDNA sequence
IT Cattle
(angiotensin II type-1 receptor **gene** of, cloning and nucleotide and encoded peptide sequences of)
IT Adrenal gland, composition
(angiotensin II type-1 receptor **gene** of, of cattle, cloning and nucleotide and encoded peptide sequences of)
IT **Gene**, animal

RL: BIOL (Biological study)
(for angiotensin II type-1 receptor, of cattle, cloning and nucleotide and encoded peptide sequences of)
IT Molecular cloning
(of angiotensin II type-1 receptor **gene**, of cattle)
IT Protein sequences
(of angiotensin II type-1 receptor, of cattle, complete)
IT Deoxyribonucleic acid sequences
(receptor-specifying, type 1, for angiotensin II, of cattle, complete)
IT Receptors
RL: BIOL (Biological study)
(type-1, for angiotensin II, **gene** for, of cattle, cloning and nucleotide and encoded peptide sequences of)
IT Animal cell line
(COS-7, cattle angiotensin II type-1 receptor **gene** expression in)
IT 7440-70-2, Calcium, biological studies
RL: BIOL (Biological study)
(COS-7 cell increase of, in angiotensin presence, after cattle angiotensin II type-1 receptor **gene** cloning)
IT 88269-39-0, **Inositol**-1,4,5-triphosphate
RL: PROC (Process)
(COS-7 cell increase of, in angiotensin presence, after cattle angiotensin II type-1 receptor **gene** cloning)
IT 138464-42-3
RL: PRP (Properties)
(amino acid sequence of)
IT 138440-38-7, Deoxyribonucleic acid (ox clone ARW angiotensin II receptor isoform AT1 messenger RNA-complementary) 138440-39-8
RL: BIOL (Biological study); PRP (Properties)
(nucleotide sequence of)
IT 11128-99-7, Angiotensin II
RL: PRP (Properties)
(receptor type-1 for, **gene** for, of cattle, cloning and nucleotide and encoded peptide sequences of)
IT 9041-90-1, Angiotensin I 9088-01-1 11130-03-3, [Sar1, Ala8]-Angiotensin II 12687-51-3, Angiotensin III 124750-99-8, Dup753
RL: PRP (Properties)
(recombinant bovine angiotensin II type-1 receptor binding by)

L5 ANSWER 8 OF 8 CAPLUS COPYRIGHT 1999 ACS
AN 1989:627531 CAPLUS
DN 111:227531
TI Four intracisternal calcium-binding glycoproteins from rat liver microsomes with high affinity for calcium. No indication for calsequestrin-like proteins in **inositol 1,4,5-trisphosphate**-sensitive calcium sequestering rat liver vesicles
AU Nguyen Van Phuc; Peter, Frank; Soeling, Hans Dieter
CS Zent. Inn. Med., Univ. Goettingen, Goettingen, D-3400, Fed. Rep. Ger.
SO J. Biol. Chem. (1989), 264(29), 17494-501
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
CC 6-3 (General Biochemistry)
AB The **inositol 1,4,5-trisphosphate**-sensitive compartment of rat liver does not contain calsequestrin-like material. Instead 4 nonmembranous Ca2+-binding glycoproteins with approx. mol. masses of 59, 60, 80, and 90 kDa were found. The 59-, 80-, and 90-kDa proteins were of the high mannose-rich type, the carbohydrate moiety of the 60-kDa protein was of the complex hybrid type with terminal galactoses. All 4 proteins had **high affinity binding** sites for Ca2+ (KD 1-5 .mu.M) and 1-5 binding sites/mol. The 80- and the 90-kDa proteins also had low affinity binding sites (KD 400 and 600 .mu.M, resp., with 13 and 15 binding sites/mol., resp.). A comparison of the N-terminal sequences revealed

that the 60-kDa Ca2+-binding protein represents the rat liver calregulin, whereas the 90-kDa Ca2+-binding protein represents grp94. The sequences did not reveal any relationship of the 80-kDa protein with grp78, or of the 59-kDa protein with protein disulfide isomerase.

ST calcium binding glycoprotein liver; calregulin calcium binding liver; **gene** grp94 glycoprotein calcium binding liver

IT Liver, composition
(calcium-binding glycoproteins of endoplasmic reticulum of)

IT Calsequestrins
RL: BIOL (Biological study)
(calcium-binding glycoproteins of liver endoplasmic reticulum in relation to)

IT Endoplasmic reticulum
(calcium-binding glycoproteins of, of liver)

IT Protein sequences
(of calregulin N terminus, of liver)

IT Conformation and Conformers
(of calregulin and grp78 glycoprotein, of liver endoplasmic reticulum)

IT Oligosaccharides
RL: BIOL (Biological study)
(of calregulin and grp94 glycoprotein, of liver endoplasmic reticulum)

IT Protein sequences
(of grp94 glycoprotein N terminus, of liver)

IT Glycoproteins, specific or class
RL: BIOL (Biological study)
(calcium-binding, 59,000-mol.-wt., of endoplasmic reticulum, of liver)

IT Glycoproteins, specific or class
RL: BIOL (Biological study)
(calcium-binding, 80,000-mol.-wt., of endoplasmic reticulum, of liver)

IT Glycoproteins, specific or class
RL: BIOL (Biological study)
(calreticulins, of endoplasmic reticulum, of liver, carbohydrate structure of and other calcium-binding glycoproteins comparison with)

IT Glycoproteins, specific or class
RL: BIOL (Biological study)
(endoplasmins, of endoplasmic reticulum, of liver, carbohydrate structure of and other calcium-binding glycoproteins comparison with)

IT 88269-39-0, **Inositol** 1,4,5-triphosphate
RL: BIOL (Biological study)
(calcium release from liver endoplasmic reticulum sensitive to, calcium-binding glycoproteins in relation to)

IT 7440-70-2, Calcium, biological studies
RL: BIOL (Biological study)

L17 ANSWER 1 OF 2 MEDLINE
AN 97303864 MEDLINE
DN 97303864
TI Binding and activity of the nine possible regioisomers of myo-**inositol** tetrakisphosphate at the **inositol 1, 4,5-trisphosphate** receptor.
AU Burford N T; Nahorski S R; Chung S K; Chang Y T; Wilcox R A
CS Department of Cell Physiology and Pharmacology, University of Leicester, UK.
SO CELL CALCIUM, (1997 Apr) 21 (4) 301-10.
Journal code: CQE. ISSN: 0143-4160.
CY SCOTLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
EW 19971001
AB All 9 racemic regioisomers (15 enantiomerically) of myo-**inositol** tetrakisphosphates (IP4s): DL-Ins(1,2,4,5)P4 [A], DL-Ins(1,2,4,6)P4 [B], Ins(1,2,3,5)P4 [C], Ins(1,3,4,6)P4 [D], Ins(2,4,5,6)P4 [E], DL-Ins(1,3,4,5)P4 [F], DL-Ins(1,2,5,6)P4 [G], DL-Ins(1,2,3,4)P4 [H] and DL-Ins(1,4,5,6)P4 [I] [Chung S-K., Chang Y-T. Synthesis of all possible regioisomers of myo-**inositol** tetrakisphosphate. J Chem Soc Chem Commun 1995; 11-13] were investigated for their ability to bind to the D-myo-**inositol 1,4,5-trisphosphate** [Ins(1,4,5)P3] receptor in bovine adrenal cortical membranes, and for their ability to mobilize 45Ca2+ from Ins(1,4,5)P3-sensitive Ca2+ stores in permeabilized Chinese hamster ovary (CHO) cells. DL-Ins(1,2,4,5)P4 (Ki = 11 nM) bound to Ins(1,4,5)P3 receptors with an affinity only 2-fold lower than Ins(1,4,5)P3 (Ki = 6 nM). Ins(1,2,3,5)P4, Ins(1,3,4,6)P4, Ins(2,4,5,6)P4, DL-Ins(1,3,4,5)P4, DL-Ins(1,2,3,4)P4 and DL-Ins(1,4,5,6)P4 bound with affinities of between 0.4-0.7 microM. DL-Ins(1,2,4,6)P4 and DL-Ins(1,2,5,6)P4 bound to the Ins(1,4,5)P3 receptor with low affinity (approximately 2-3 microM). All but one of the IP4s mediated release of 45Ca2+ from stores of permeabilized CHO cells with a similar rank order of potency as that for Ins(1,4,5)P3 receptor binding, being between 16-fold and 50-fold less potent at releasing 45Ca2+ compared with their apparent binding affinities to the Ins(1,4,5)P3 receptor. The notable exception was Ins(1,2,3,5)P4, which showed an approximately 200-fold lower potency compared with its affinity for the Ins(1,4,5)P3 receptor. Ins(1,2,3,5)P4 may be a useful lead compound for the rational design of novel synthetic Ins(1,4,5)P3 analogues possessing structure-activity profiles with relatively **high binding** affinity, but low intrinsic efficacy, and hence partial agonists and antagonists at the Ins(1,4,5)P3 receptor.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Calcium: ME, metabolism
*Calcium Channels: ME, metabolism
Cattle
Cell Membrane Permeability
CHO Cells
Hamsters
***Inositol Phosphates: ME, metabolism**
Ionomycin: PD, pharmacology
Ionophores: PD, pharmacology
Isomerism
Models, Chemical
*Receptors, Cytoplasmic and Nuclear: ME, metabolism
RN **102850-29-3 (inositol-1,3,4,5-tetrakisphosphate)**; 56092-81-0

(Ionomycin); 7440-70-2 (Calcium)
CN 0 (**inositol**-1,4,5-triphosphate receptor); 0 (Calcium Channels); 0 (**Inositol** Phosphates); 0 (Ionophores); 0 (Receptors, Cytoplasmic and Nuclear)

L17 ANSWER 2 OF 2 MEDLINE
AN 96074809 MEDLINE
DN 96074809
TI Molecular cloning and expression of multiple isoforms of human prostaglandin E receptor EP3 subtype generated by alternative messenger RNA splicing: multiple second messenger systems and tissue-specific distributions.
AU Kotani M; Tanaka I; Ogawa Y; Usui T; Mori K; Ichikawa A; Narumiya S; Yoshimi T; Nakao K
CS Department of Medicine, Faculty of Medicine, Kyoto University, Japan.
SO MOLECULAR PHARMACOLOGY, (1995 Nov) 48 (5) 869-79.
Journal code: NGR. ISSN: 0026-895X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-D38297; GENBANK-D38298; GENBANK-D38299; GENBANK-D38300; GENBANK-D38301
EM 199602
AB Five distinct cDNA clones encoding four different isoforms of human prostaglandin (PG) E receptor EP3 subtype were isolated from a human kidney cDNA library. Two cDNA clones differed only in their 3'-untranslated regions. The four isoforms, tentatively named EP3-I, EP3-II, EP3-III, and EP3-IV, which were generated by alternative mRNA splicing, had identical amino acid sequences except for their different carboxyl-terminal tails. Transfection experiments revealed that all the four isoforms show **high binding** affinities to PGE2, PGE1, and M&B28767, an EP3-specific agonist, whereas their downstream signaling pathways are divergent. M&B28767 increased cAMP concentrations in cells expressing EP3-II and EP3-IV, whereas it inhibited forskolin-induced cAMP accumulations in cells expressing all EP3 isoforms.
M&B28767 also stimulated phosphoinositide turnover in cells expressing EP3-I and EP3-II. Northern blot analysis revealed that the EP3 gene is expressed in a wide variety of human tissues. The human EP3 mRNA was present most abundantly in the kidney, pancreas, and uterus. A substantial expression was also detected in the heart, liver, skeletal muscle, small intestine, colon, prostate, ovary, and testis. Furthermore, reverse transcription-polymerase chain reaction analysis demonstrated tissue-specific expressions of the five different EP3 mRNA species. The present study suggests the presence of the multiple systems of PGE2/EP3 isoforms and leads to the better understanding of its physiological and pathophysiological implications in humans.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
*Alternative Splicing
Amino Acid Sequence
Base Sequence
Blotting, Northern
Blotting, Southern
Cloning, Molecular
Cyclic AMP: AN, analysis
CHO Cells
Dinoprostone: ME, metabolism
Hamsters
Inositol 1,4,5-Trisphosphate: AN, analysis
Molecular Sequence Data
Organ Specificity
Polymerase Chain Reaction
Receptors, Prostaglandin E: CH, chemistry
*Receptors, Prostaglandin E: GE, genetics

Receptors, Prostaglandin E: PH, physiology
*Second Messenger Systems
*Second Messenger Systems: PH, physiology
RN 363-24-6 (Dinoprostone); 60-92-4 (Cyclic AMP); **85166-31-0 (Inositol 1,4,5-Trisphosphate)**
CN 0 (Receptors, Prostaglandin E)

29 ANSWER 1 OF 3 MEDLINE
AN 1999119984 MEDLINE
DN 99119984
TI Interaction of the Na(+)-Ca2+ exchanger with small molecules on cell Ca2+ signaling.
AU Fang Y; Rong M; He L
CS Department of Anesthesiology, Zhong Shan Hospital, China.
SO BIOMEDICINE AND PHARMACOTHERAPY, (1998) 52 (10) 459-64.
Journal code: A59. ISSN: 0753-3322.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199906
EW 19990603
AB Interactions of the Na(+)-Ca2+ exchanger with small molecules on cell Ca2+
signaling were elucidated in Chinese hamster ovary (CHO) C1 cells, which transfected a control **vector** without any expression of the Na(+)-Ca2+ exchanger's gene while CHO CK1.4 cells transfected an expression **vector** encoding the bovine cardiac Na(+)-Ca2+ exchanger's cDNA, treated with lithium- or sodium-buffer medium respectively, by using L16(2)15 multifactorial orthogonal statistics and fura-2 fluorescence real-time imaging. In contrast to controls of Li(+)-treated C1 cells, the store-dependent Ca(2+)-influx (SDCI) was enhanced by either the Na(+)-Ca2+ exchanger, Na(+), 1-{(beta-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl}-1H-imidazole HCl (SK&F96365) or
ouabain, and by interactions of the Na(+)-Ca2+ exchanger with either Na+, SK&F96365 or both SK&F96365 and ouabain; and ATP-induced Ca2+ release (AICR) was activated by SK&F96365 or Na+ alone, interactions of the Na(+)-Ca2+ exchanger with SK&F96365 or Na+, and an interaction between SK&F96365 and ouabain. The dramatic interaction of the Na(+)-Ca2+ exchanger with small molecules indicates that cell Ca2+ signaling is generated by **inositol** triphosphate (InsP3)-dependent pathways, allosteric effects of the G-protein coupled P2y&2u purinoceptor and multi-site recognition. Our findings provide meaningful clues for designing new strategies of cardiocerebral vascular oxidative **diseases.**
CT Check Tags: Animal; Support, Non-U.S. Gov't
Adenosine Triphosphate: PD, pharmacology
*Calcium Signaling: PH, physiology
CHO Cells
Fluorescent Dyes
Fura-2
Hamsters
Indicators and Reagents
*Sodium-Calcium Exchanger: PH, physiology
RN 56-65-5 (Adenosine Triphosphate); 96314-98-6 (Fura-2)
CN 0 (Fluorescent Dyes); 0 (Indicators and Reagents); 0 (Sodium-Calcium Exchanger)

L29 ANSWER 2 OF 3 MEDLINE
AN 94253977 MEDLINE
DN 94253977
TI Correlation of phosphoinositide hydrolysis with exflagellation in the malaria microgametocyte.
AU Martin S K; Jett M; Schneider I
CS Department of Molecular Pathology, Walter Reed Army Institute of Research,

Washington, DC 20307-5100.
SO JOURNAL OF PARASITOLOGY, (1994 Jun) 80 (3) 371-8.
Journal code: JL3. ISSN: 0022-3395.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199409
AB Cellular responses to growth factors, hormones, and other agonists have been shown in many animal cell systems to be mediated by the signal transduction cascade controlled by phospholipase C. One such response, calcium mobilization, is regulated by the concerted effect of several specific **inositol** (poly)phosphates. Another response, protein phosphorylation, is regulated by other phospholipase C (PLC) hydrolysis products. Mature gametocytes are specialized cells primed for transformation into gametes immediately upon removal from the vertebrate bloodstream, thereby initiating the sexual cycle in a **vector** mosquito. This study showed that PLC hydrolysis products, **inositol** (1,4,5)triphosphate and diacylglycerol, are correlated with the initial events of flagellar development; they are implicated in synchronizing this
crucial transformation for the parasite and hence the continued transmission of the parasite, which leads to this debilitating **disease.**
CT Check Tags: Animal
Chromatography, High Pressure Liquid
Culture Media
Diglycerides: ME, metabolism
Diglycerides: PH, physiology
*Flagella: PH, physiology
Hydrolysis
Inositol 1,4,5-Trisphosphate: ME, metabolism
Inositol 1,4,5-Trisphosphate: PH, physiology
Kinetics
Microscopy, Phase-Contrast
*Phosphatidylinositols: ME, metabolism
Phospholipase C: PH, physiology
Plasmodium falciparum: ME, metabolism
*Plasmodium falciparum: PH, physiology
Plasmodium falciparum: UL, ultrastructure
Signal Transduction
Substrate Specificity
RN **85166-31-0 (Inositol 1,4,5-Trisphosphate)**
CN EC 3.1.4.3 (Phospholipase C); 0 (Culture Media); 0 (Diglycerides); 0 (Phosphatidylinositols)

L29 ANSWER 3 OF 3 MEDLINE
AN 94018073 MEDLINE
DN 94018073
TI Multiple regression of skeletal muscle tension on **inositol** phosphates: cross-talk between signal transduction mechanisms in burn trauma.
AU Tomera J F; Lilford K
CS Clinical Pharmacology Laboratory, Shriners Burn Institute, Boston, MA.
SO METHODS AND FINDINGS IN EXPERIMENTAL AND CLINICAL PHARMACOLOGY, (1993 Jun)
15 (5) 255-65.
Journal code: LZN. ISSN: 0379-0355.
CY Spain
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199401
AB Skeletal muscle weakness associated with burn trauma prolongs the time of rehabilitation of burn patients. Understanding the underlying chemical changes that impact on physiological tension may provide new therapeutic

options for the treatment of burn patients. This report demonstrates the novelty of applying 3-dimensional graphic capabilities, involving area and **vector** changes to understand variations in **inositol** derivatives and their co-modulating influence on physiological tension in skeletal muscle. This muscle was distant from the primary anatomical burn site. It was subjected to circulatory shock emanating from burn trauma. Burn injury was achieved by scalding of predefined areas (0, 20% and 50%) on the dorsal and ventral surfaces of mice. At day 21, tension studies via muscle twitch analyses were performed. Through multiple regression, the dependency of physiologic tension was determined with respect to three poly-**inositol** forms each representing independent parameters simultaneously. The contribution of each of these parameters was assigned to a three-dimensional axis. Relationships of tension on three fixed independent parameters were found only for the 20% and 50% burn groups. **Vector** analysis on a plane in three-dimensional space determined the relationship of tension to each of the independent parameters in 20% and 50% burn groups. No significant relationship of tension dependency on three fixed poly-**inositol** variables was found in the control group. Such **vector** analysis, using solid and differential analytical geometry, allowed for a clear visualization of the interrelationships that existed between secondary messenger systems (viz, IP3) and a resulting physiologic manifestation (viz, tension). This clear visualization allows for a greater understanding of messenger systems that may lead to more effective treatment of skeletal muscle weakness associated with the systemic effects of severe burn trauma.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
Burns: ME, metabolism
*Burns: PP, physiopathology
Disease Models, Animal
Inositol Phosphates: ME, metabolism
***Inositol Phosphates: PH, physiology**
Inositol 1,4,5-Trisphosphate: ME, metabolism
Inositol 1,4,5-Trisphosphate: PD, pharmacology
Mice
Mice, Inbred Strains
Multivariate Analysis
Muscle Contraction: DE, drug effects
Muscle Contraction: PH, physiology
Muscles: DE, drug effects
Muscles: ME, metabolism
*Muscles: PP, physiopathology
Regression Analysis
*Signal Transduction: PH, physiology

RN **85166-31-0 (Inositol 1,4,5-Trisphosphate)**

CN 0 (**Inositol** Phosphates)